

# Re. KC Wilhelmsen, M Schuckit *et al* (2003): The search for genes related to a low-level response to alcohol determined by alcohol challenges

M Soyka

Munich, Germany

*The Pharmacogenomics Journal* (2004) 4, 3–4. doi:10.1038/sj.tpj.6500228

There is overwhelming evidence for genes to play a substantial role in the development of alcoholism. Of the population variance for alcoholism, 50–60% vulnerability may be explained by genes.<sup>1</sup> In addition, patterns of alcohol use seem to be under the genetic influence. Evidence comes from clinical, epidemiological, twin<sup>2</sup> and especially adoption studies, among others. The question is: what is inherited? The vulnerability to develop alcoholism may be mediated by variances in alcohol-metabolizing enzymes or alcohol tolerance, variations in neurotransmission, or personality dimensions such as impulsivity or aggression. Many other variables could be mentioned. There is broad consensus that as in other fields of psychiatry genetics, it is most unlikely that a single or a few genes are responsible for most of the variance.

In the recent decade, substantial effort was made to elucidate genetic mechanisms involved in the transmission of the vulnerability risk for alcoholism. One of the most ambitious projects in this field is the US Collaborative Study on the Genetics of Alcoholism (COGA).<sup>3,4</sup> In brief, it is an extensive family study with hundreds of affected and unaffected families studied so far. Beside the genome search for markers, COGA is

interested in neurophysiological (evoked potentials) and other markers for alcoholism. Substantial effort is made to phenotype patients carefully with respect to family and alcohol history, comorbidity with other psychiatric disorders and personality dimensions. The impact of research instruments development by the COGA group is substantial and many of the diagnostic instruments applied like the Semi-Structured Assessment for the Genetics of Alcoholism<sup>5</sup> have been translated in other languages and are used as research instruments in the field.<sup>6</sup> They are also part of the diagnostic procedure of the recent study by Wilhelmsen *et al.*<sup>7</sup> To date, despite the substantial efforts in this area, the genomic search for vulnerability markers for alcoholism has at least produced conflicting results. There is tremendous effort in studying possible candidate genes for alcoholism but there are no final answers yet.<sup>8</sup>

One of the best-examined hypothesis is the predictive value of the individual response to alcohol for the later development of alcoholism. Genetic effects on patterns of alcohol use have been demonstrated already for the adolescence.<sup>9</sup> It is fair to say that this for decades has been the major research interest of the second author of the paper, Marc Schuckit, who in a number of impressive experimental and follow-up studies has demonstrated that a person's level of response (LR) to alcohol has a great

impact for the subsequent risk for alcohol-related problems including alcohol dependence.<sup>10,11</sup> Most but not all studies<sup>12</sup> point in that direction.

The study by Wilhelmsen *et al.*<sup>7</sup> is a further extension of this hypothesis. In brief, the authors report results of a genome-wide segregation analysis of the first 139 pairs of full siblings by using an alcohol challenge protocol as a direct measure of LR. The data are somehow preliminary since the database will be expanded significantly. In these individuals (age 18–29, no evidence for alcohol dependence) body sway and Subjective High Assessment Scale scores were measured at baseline and at regular intervals after the administration of a measured dose of alcohol (20% by volume solution of 0.75 ml/kg of 95% ethanol for women and 0.90 ml/kg for men). Participants and available parents were genotyped for 811 microsatellite markers, and the resulting data were analyzed with a variance component method. Results indicate that nine chromosome regions with LOD scores between 2.2 and 3.2 were identified and several regions identified in a previous linkage study were potentially confirmed by this study. The strongest evidence was on chromosomes 10.11 and 22. For some of the chromosome loci candidate genes are named, for example, serotonin 1D receptor, cannabinoid receptor, opioid receptor (chromosome 1) or different GABA receptor subunits (chromosome 4).

I will not discuss the methodological and statistical pitfalls of genome-wide linkage analysis with respect to alcoholism but will rather make two specific comments to this exciting study. Wilhelmsen *et al.*<sup>7</sup> themselves point out there is no consensus as to which is the best analytical approach.

First, it is essential to notice that results relate to behavioral consequences of exposure to moderate doses of alcohol only. This makes sense clinically but higher doses of alcohol may show different results. Second, even more important is that two very

different variables were studied: a neurological symptom, changes in body sway and subjective responses (SHAS scores). Other possible parameters (eg, neuroendocrinological or neurophysiological parameters) were not part of this study. Apart from the question as to whether these two parameters and a single testing are sufficient to characterize an individual's response to alcohol, it seems highly unlikely that these two variables relate to the same genetic loci. Not surprisingly, in the genome analysis *either* body sway or SHAS were linked to a specific chromosome region, in no case both together. This may not come as a surprise—a chromosome region linked to both would be sensational—but illustrates the heterogeneity of the response-to-alcohol concept.

Wilhelmsen *et al*<sup>7</sup> point out that among five regions cited by COGA with respect to a possible linkage finding for alcohol dependence, four may relate to the SHAS or body sway findings. Future studies will address the possible role of the serotonin transporter and the GABAR subunit alpha6, or others.

A final comment to what is consistently overlooked in studies looking at the subjective response to alcohol and its effect as a risk factor for alcoholism.

There are very probable not only predisposing but also protective genes reducing the risk for alcohol. This has nearly exclusively been discussed with respect to variances in alcohol metabolizing enzymes (ADH, ALDH). There is extensive literature on this issue.<sup>13</sup>

Without ignoring the significant problems in defining possible protective factors clinically (eg looking at individuals in affected families who do *not* develop alcoholism), this may be an alternate approach that might be worth a thought.

#### DUALITY OF INTEREST

None declared

#### Correspondence should be addressed to:

Professor Dr M Soyka,  
Tel.: + 49 89 5160 5324/2777  
Fax: + 49 89 5160 5617

#### REFERENCES

- 1 Mc Gue M. The behavioural genetics of alcoholism. *Curr Dir Psychol Sci* 1999; **8**: 109–115.
- 2 Heath AC. Genetic influences on drinking behavior in humans. In: Begleiter H, Kissin B (eds). *The Genetics of Alcoholism*. Oxford University Press: New York 1995: 82–121.
- 3 Reich T, Edenberg HJ, Goate A, Williams JT, Rice JP *et al*. Genome-wide search for genes affecting the risk for alcohol dependence. *Am J Med Genet* 1998; **81**: 207–215.
- 4 Nurnberger JI Jr, Foroud T, Flury L, Su J, Meyer ET, Hu K *et al*. Evidence for a locus on chromosome 1 that influences vulnerability

- to alcoholism and affective disorder. *Am J Psychiatry* 2001; **158**: 718–724.
- 5 Hesselbrock M, Easton C, Bucholz KK, Schuckit M, Hesselbrock V. A validity study of the SSAGA—a comparison with the SCAN. *Addiction* 1999; **94**: 1361–1370.
- 6 Soyka M, Preuss UW, Koller G, Zill P, Bondy P. Dopamine D4 receptor polymorphism in extraversion revisited: results from the Munich Gene Bank Project for Alcoholism. *J Psychiatry Res* 2002; **36**: 429–435.
- 7 Wilhelmsen KC, Schuckit M, Smith TL, Lee JV, Segall SK *et al*. The search for genes related to a low-level response to alcohol determined by alcohol challenges. *Alcohol Clin Exp Res* 2003; **27**: 1041–1047.
- 8 Dick D, Foroud T. Candidate genes for alcohol dependence: a review of genetic evidence from human studies. *Alcohol Clin Exp Res* 2003; **27**: 868–879.
- 9 Rose RJ, Dick DM, Viken RJ, Kaprio J. Gene-environment interaction in patterns of adolescent drinking: regional residency moderates longitudinal influences on alcohol use. *Alcohol Clin Exp Res* 2001; **25**: 637–643.
- 10 Schuckit MA, Smith TL. An 8-year follow-up of 450 sons of alcoholic and control subjects. *Arch Gen Psychiatry* 1996; **53**: 202–210.
- 11 Schuckit MA, Smith TL. The relationships of family history of alcohol dependence, a low level of response to alcohol and six domains of life functioning to the development of alcohol use disorders. *J Stud Alcohol* 2000; **61**: 827–835.
- 12 Vogel-Sprott M, Chipperfield B. Family history of problem drinking among young male social drinkers: behavioral effects of alcohol. *J Stud Alcohol* 1987; **48**: 430–436.
- 13 Agarwal DP. Genetic polymorphisms of alcohol metabolizing enzymes. *Pathol Biol* 2001; **49**: 703–709.